DOCUMENT-IDENTIFIER: US 5665591 A
TITLE: Regulation of smooth muscle cell proliferation

Brief Summary Paragraph Right (13):
A number of agents which affect cell proliferation have been tested as pharmacological treatments for stenosis and restenosis in an attempt to slow or inhibit proliferation of SMCs. These compositions have included heparin, coumarin, aspirin, fish oils, calcium antagonists, steroids, prostacyclin, rapamycin, dipryidamole, ultraviolet irradiation, gamma (.gamma.)-interferon, serotonin inhibitors, methotextrate and mycophenolic acid, either alone or in various combinations. For example, heparin is commonly used following coronary angioplasty to reduce the incidence of acute thrombotic occlusion and reduce the proliferation of SMCs (Guyton et al., Circ. Res. 46:625, 1980). These activities were demonstrated in vitro and confirmed in vivo in experiments on rat arterial SMC proliferation after balloon catheter injury (Gordon et al., Circulation 76:213, 1987). Wai et al. determined that a hybrid protein consisting of the ribosome inhibitor, saponin, fused to basic fibroblast growth factor (FGF), killed proliferating FGF-receptor expressing SMCs, but not quiescent receptor negative cells (Wai et al., Circulation 82:208, 1990). This same hybrid protein also inhibited intimal thickening following vascular injury.

Brief Summary Paragraph Right (19):
Local delivery has also been achieved with the use of catheters (U.S. Pat. No. 4,636,195), stents (U.S. Pat. No. 5,304,121), coatings on balloon catheters (U.S. Pat. No. 5,102,402), direct injection of the agent formulated with a biodegradable polymer (U.S. Pat. No. 5,171,217), and hydrogel polymer/agent coatings on catheters. These anti-thrombogenic and anti-proliferative agents have demonstrated limited successes.

Detailed Description Paragraph Right (10):
Another embodiment of the invention is directed to compositions comprising SMC-TF or a SMC-TF-like factor, active fragments of these proteins or fusion proteins containing some portion of a factor, and a pharmaceutically acceptable carrier. Active fragments are those portions of the entire protein which have a substantial amount of the biological or physical activity of the entire protein or parts thereof. Appropriate carriers are determined by the route of administration of the factor and include water, oils, fatty acids, alcohols, salts, saccharides, polysaccharides, celluloses, starches and combinations of these carriers. Compositions may be prepared in a variety of formulations including tablets, coated tablets, capsules, granules, aerosols, syrups, emulsions, suspensions, solutions, and ointments with pharmaceutically acceptable excipients, solvents or slow release polymers and the like.

Detailed Description Paragraph Right (18):
Local or site-directed delivery of oligonucleotides or any agent can be performed by injection, pulmonary absorption, oral ingestion, topical application, macromolecular targeting using conjugates and fusion proteins, and immediate or coordinated release from implants. Useful implantable devises include catheters, stents or coated articles placed into the host. Continuous application can be achieved through the use of the selected formulations on the implants which delay the release or provide a timed-release of the agent. The activity of agents can be enhanced through binding to other molecules. For example, an oligonucleotide can be conjugated to a ligand which, when receptor bound, is endocytosed into the cell. Alternatively, oligonucleotides may be bound to vasodilators, anti-thrombogenic reagents and the like. SMC-TF activity may also be inhibited using anti-oxidants or reducing agents. Such reagents can be formulated and delivered either systemically or locally. SMC-TF activity can also be inhibited using inhibitor proteins or active portions or fragments of these proteins. Proteins which inhibit SMC-TF include I.kappa.B and its

variants, I.kappa.B-.alpha. (MAD-3), I.kappa.B-.beta., I.kappa.B-.gamma., pp40, Bcl-3, the dominant negative p50 (I-rel), and various antibodies.

DOCUMENT-IDENTIFIER: US 5932243 A
TITLE: Galenical formulations

Abstract Paragraph Left (1):
A pharmaceutical composition containing macrolide, e.g. a rapamycin compound in an emulsion preconcentrate or microemulsion preconcentrate for oral administration. The carrier medium for the rapamycin compound includes a hydrophilic phase, a lipophilic phase and a surfactant. The composition is stable and provides high absorption efficiency.

Brief Summary Paragraph Right (1):
This invention relates to galenic formulations containing macrolides, e.g. compounds of the rapamycin class. In particular this invention relates to galenic formulations which are in the form of micro-emulsions, micro-emulsion preconcentrates, emulsion or emulsion-preconcentrate.

Brief Summary Paragraph Right (3):
Rapamycin is a macrolide antibiotic produced by Streptomyces hygroscopicus. It has been found to be pharmaceutically useful in a variety of applications, particularly as an immunosuppressant for use in the treatment and prevention of organ transplant rejection and autoimmune diseases. Rapamycin has the following structure: ##STR1##

Brief Summary Paragraph Right (4):
(Kesseler, H., et al., Helv. Chim. Acta (1993) 76: 117; U.S. Pat. No. 3,929,992). Large numbers of derivatives of rapamycin have been synthesized, including for example those disclosed in U.S. Pat. Nos. 5,221,670 and 5,221,740, certain acyl and aminoacyl-rapamycins (see for example U.S. Pat. No. 4,316,885, U.S. Pat. No. 4,650,803, and U.S. Pat. No. 5,151,413), and carbonates and amide esters (see for example EP 509795 and 515140) 27-desmethyl-rapamycin (see for example WO 92/14737), 26-dihydro-rapamycin (see for example U.S. Pat. No. 5,138,051), alkoxyester derivatives (see for example U.S. Pat. No. 5,233,036), and certain pyrazole derivatives (U.S. Pat. No. 5,164,399). Rapamycin and its structurally similar analogs and derivatives are termed collectively as "compounds of the rapamycin class" in this specification.

Brief Summary Paragraph Right (5):
Compounds of the rapamycin class are extremely potent immunosuppressants and have also been shown to have antitumor and antifungal activity. However their utility as pharmaceuticals especially on oral administration has been restricted by their very low solubility, low and variable bioavailability and their high toxicity. Little is known concerning the causes of these properties and the site of absorption. Thus low bioavailability may be thought to due to due to extensive metabolism of the macrolide ring and not solvable by a galenical formluation.

Brief Summary Paragraph Right (6):
Therefore there is a need for an acceptable pharmaceutical composition that contains compounds of the rapamycin class.

Brief Summary Paragraph Right (21):
The macrolide may be rapamycin or an O-substituted derivative in which the hydroxy in position 40 of the formula illustrated above is replaced by --OR.sub.1 in which R.sub.1 is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. These O-substituted derivatives may be produced by reacting Rapamycin (or dihydro or deoxorapamycin) with an organic radical attached to a leaving group (for example RX where R is the organic radical which is desired as the O-substituent, such as an alkyl, allyl, or benzyl moiety, and X is a leaving group such as CCl.sub.3 C(NH)O or

CF.sub.3 SO.sub.3) under suitable reaction conditions. The conditions may be acidic or neutral conditions, for example in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is CCl.sub.3 C(NH)O or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF.sub.3 SO.sub.3.

Brief Summary Paragraph Right (22):
A preferred compound is 40-O-(2-hydroxy)ethyl rapamycin (hereinafter compound A) as disclosed in PCT/EP/93/02604.

Brief Summary Paragraph Right (25):
The hydrophilic phase may be selected from Transcutol (which has the formula C.sub.2 H.sub.5 --[O--(CH.sub.2).sub.2].sub.2 --OH), Glycofurol (also known as tetrahydrofurfuryl alcohol polyethylene glycol ether) and 1,2-propylene glycol, or mixtures thereof, and is preferably 1,2-propylene glycol. The hydrophilic phase may include further hydrophilic co-components, for example lower alkanols such as ethanol. These co-components will generally be present in partial replacement of other components of the hydrophilic phase. While the use of ethanol in the compositions is not essential, it has been found to be of particular advantage when the compositions are to be manufactured in soft gelatine, encapsulated form. This is because storage characteristics are improved, in particular the risk of rapamycin precipitation following encapsulation procedures is reduced. Thus the shelf life stability may be extended by employing ethanol or some other such co-component as an additional ingredient of the hydrophilic phase. The ethanol may comprise 0 to 60% by weight of the hydrophilic phase; preferably 20 to 55% by weight and more preferably about 40 to 50% by weight. Small quantities of liquid polyethylene glycols may also be included in the hydrophilic phase.

Brief Summary Paragraph Right (49):
The pharmaceutical composition may also include one or more other immunosuppressants such as, for example, a cyclosporin or if a rapamycin is present a FK506 compound as described above. Cyclosporins comprise a class of cyclic, poly-N-methylated undecapeptides, generally possessing immunosuppressive, anti-inflammatory, anti-viral and/or anti-parasitic activity, each to a greater or lesser degree. The first of the cyclosporins to be identified was the fungal metabolite Cyclosporin A, or Ciclosporine, and its structure is given in The Merck Index, 11th Edition; Merck & Co., Inc.; Rahway, N.J., USA (1989) under listing 2759. Later cyclosporins to be identified are cyclosporins B, C, D and G which are also listed in the Merck Index under listing 2759. A large number of synthetic analogs are also known and representative examples are disclosed in EP 296 122, EP 484 281 and GB 2222770. These compounds are termed collectively "cyclosporins" in this specification.

Brief Summary Paragraph Right (50):
The pharmaceutical composition exhibits especially advantageous properties when administered orally; for example in terms of consistency and high level of bioavailability obtained in standard bioavailability trials, e.g. 2 to 4 times higher than emulsions. These trials are performed in animals or healthy volunteers using HPLC or a specific or nonspecific monoclonal kit to determine the level of the macrolide in the blood. For example, in the test described in Example 3, 10 mg of rapamycin is administered p.o. to rats and the surprisingly high C.sub.max values of between 2670 and 3400 ng/ml are detected by ELISA using a specific monoclonal antibody. Also, in the test described in Example 4, an emulsion preconcentrate and a microemulsion preconcentrate composition are found to have much better pharmacokinetic properties than a standard solvent system.

Brief Summary Paragraph Right (55):
The optimal dosage of macrolide to be administered to a particular patient must be considered carefully by the treating physician as individual response to and metabolism of the rapamycin compound may vary. It may be advisable to monitor the blood serum levels of the rapamycin compound by radioimmunoassay, monoclonal antibody assay, or other appropriate conventional means. Dosages of the macrolide will generally range from 2.5 mg to 1000 mg per day for a 75 kilogram adult, preferably 25 mg to 500 mg, with the optimal dosage being approximately 50 to 100 mg per day. Satisfactory results are obtained by administering about 75 mg per day for example in the form of two capsules, one containing 50 mg and one containing 25 mg; or three capsules each containing 25 mg. If a cyclosporin or FK506 compound is included in the pharmaceutical composition, the cyclosporin dosage may be 25 to 1000 mg per day (preferably 50 mg to 500 mg) and the FK506 compound dosage may be 2.5 mg

to 1000 mg per day (preferably 10 mg to 250 mg).

Brief Summary Paragraph Right (57):
The rapamycin compounds also exhibit anti-tumour and antifungal activity and hence the pharmaceutical compositions can be used as anti-tumour and anti-fungal agents.

Brief Summary Paragraph Right (62):
The following examples illustrate compositions in unit dosage form, suitable for use, for example in the prevention of transplant rejection or for the treatment of autoimmune disease, on administration of from 1 to 5 unit dosages/day. The examples are described with particular reference to rapamycin but equivalent compositions may be obtained employing any other macrolide.

Brief Summary Paragraph Type 1 (21):
a) The treatment and prevention of organ or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants. The pharmaceutical compositions are also indicated for the prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation.

Brief Summary Paragraph Type 1 (24):
d) The treatment of multi-drug resistance (MDR). The rapamycin compounds suppress P-glycoproteins (Pgp), which are the membrane transport molecules associated with MDR. MDR is particularly problematic in cancer patients and AIDS patients who will not respond to conventional chemotherapy because the medication is pumped out of the cells by Pgp. The pharmaceutical compositions are therefore useful for enhancing the efficacy of other chemotherapeutic agents in the treatment and control of multidrug resistant conditions such as multidrug resistant cancer or multidrug resistant AIDS.

Detailed Description Paragraph Right (5):
The rapamycin is suspended in (1) with stirring at room temperature and (2), (3) and (4) are added to the obtained solution while stirring. The obtained mixture is filled into size 0 hard gelatine capsules and sealed using the Quali-Seal technique.

Detailed Description Paragraph Right (7):
Formulation A is an emulsion preconcentrate and formulation B is a microemulsion preconcentrate. 6 male Wistar rats of mean body weight of 300 g are used per form. One day before treatment, food is withdrawn from the rats but the rats are permitted free access to water. The rats are then anesthetized by intraperitoneal injection of 2.times.1 ml 20% urethane and a permanent catheter is inserted into the right vena jugularis to permit blood sampling. 500 ml/animal of the formulation is administered by gastric intubation 20 hours after the surgery. A total dose of 10 mg of drug per animal is administered. Blood samples of 0.7 ml are taken from the jugular catheter of each animal 15 minutes before drug administration and then 0.17, 0.5, 1, 1.5, 2, 3, 5 and 8 hours after drug administration. The samples are kept in heparinized tubes and are analysed by means of ELISA using microtitre plates coated with rapamycin specific antibodies. The animals are killed immediately after taking the last blood sample. The results are given in the following table:

Detailed Description Paragraph Right (8):
The results indicate that rapamycin is well absorbed.

Detailed Description Paragraph Right (9):
Formulations A and B are compared to a formulation comprising 38.6% corn oil, 41.6% Labrafil M21/25C, 17.8% ethanol and 2% rapamycin (formulation C). The same procedure as used in example 3 is used except that the animals each receive a total dose of 0.5 mg of drug.

Detailed Description Paragraph Right (12):
An active compound of the FK506 class or rapamycin class e.g. compound A is made up into a microemulsion preconcentrate having the following composition by weight 2% active compound 44% Cremophor RH40 26.4% corn-oil mono-, di-, tri-glycerides, 17.6% 1,2 propylene glycol and 10% ethanol.

Detailed Description Paragraph Table (1):

QUANTITY COMPONENT (mg/capsule)	
Rapamycin 20.0 1)	Ethanol 75.0 2)

1,2-propylene glycol 81.0 3) refined oil 121.5 3) Cremophor RH40 202.5 Total 500.0

Detailed Description Paragraph Table (2):

Formulation Component Amount %

A Tween 80 41.5% Maisine 24.90% Propylene glycol 16.6% Ethanol 15.0% Rapamycin 2.0% B Cremophor RH40 41.5% Maisine 24.9% Propylene glycol 16.6% Ethanol 15.0% Rapamycin 2.0%

CLAIMS:

1. A pharmaceutical composition for oral administration which is a microemulsion preconcentrate comprising 40-O-(2-hydroxy)ethyl rapamycin as active ingredient in a carrier medium which comprises

i) a hydrophilic component, which, with co-components, if present, comprises 10 to 50% by weight of the carrier medium and which is Transcutol, Glycofurol, 1,2-propylene glycol, or mixtures thereof;

ii) a lipophilic component, which comprises 10 to 85% by weight of the carrier medium and which is selected from the group consisting of 1) fatty acid triglycerides, 2) mixed mono-, di-,and tri-glycerides, and 3) transesterified ethoxylated vegetable oils; and

iii) a surfactant, which comprises 5 to 80% by weight of the carrier medium and which is selected from the group consisting of polyethyleneglycol, natural or hydrogenated castor oils, polyethylene-sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene-polyoxypropylene co-polymers, and block co-polymers

the relative proportion of the active ingredient and components i), ii) and iii) being such that on dilution with water, a microemulsion having an average particle size of <1,500 .ANG. is spontaneously formed.

DOCUMENT-IDENTIFIER: US 6153252 A
TITLE: Process for coating stents

Abstract Paragraph Left (1):
A process is provided for coating stents having a first and second surface with passages there between to avoid blockage and bridging of the passages. The process comprises contacting the stent with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent while maintaining a fluid flow through said passages sufficient prevent the film forming biocompatible polymer from substantially blocking said passages. Also described are stents coated by this process.

Parent Case Paragraph Right (1):
This application claims benefit from U.S. Provisional Application No. 60/091,217 filed Jun. 30, 1998, which is hereby incorporated by reference herein. The invention relates generally to a process for coating surgical devices. More specifically this invention relates to an improved process for coating stents and the like.

Brief Summary Paragraph Right (1):
Stents, which are generally open tubular structures, have become increasingly important in medical procedures to restore the function of body lumens. Stents are now commonly used in translumenial procedures such as angioplasty to restore an adequate blood flow to the heart. However, stents may stimulate foreign body reactions that result in thrombosis or restenosis. To avoid these complications a variety of stent coatings and compositions have been proposed in the literature both to reduce the incidence of these complications or other complications and restore tissue function by itself or by delivering therapeutic compound to the lumen.

Brief Summary Paragraph Right (2):
Stents generally are coated by simple dip or spray coating of the stent with polymer or polymer and a pharmaceutical/therapeutic agent or drug. These methods are acceptable for early stent designs that were of open construction fabricated from wires (Wiktor stent) or from ribbons (Gianturco). Dip coating with relatively low coating weights (about 4% polymer) could successfully coat such stents without any problems such as excess coating bridging (i.e. forming a film across) the open space between structural members of the device. This bridging is of particular concern when coating more modern stents that are of less open construction, such as the Palmaz-Schatz, Crown, Multilink or GFX stents. Bridging of the open space (slots) is undesirable because it can interfere with the mechanical performance of the stent, such as expansion during deployment in a vessel lumen. Bridges may rupture upon expansion and provide sites that activate platelet deposition by creating flow disturbances in the adjacent hemodynamic environment or pieces of the bridging film may break off and cause further complications. Bridging of the open slots may also prevent endothelial cell migration complicating the endothelial cell encapsulation of the stent.

Brief Summary Paragraph Right (3):
Similarly, spray coating can be problematic in that there is a significant amount of spray lost during the process and many of the pharmaceutical agents that one would like to incorporate in the device are quite costly. In addition, in some cases it would be desirable to provide coated stents with high levels of coating and drug. High concentration coatings (.about.15% polymer with additional drug) are the preferred means to achieve high drug loading. Multiple dip-coating has been described in the literature as a means to build thicker coatings on the stent. However, composition and phase dispersion of the pharmaceutical agents affect sustained release. In addition, the application of multiple dip coats from low concentration solutions often has the effect of reaching a limiting loading level as

an equilibrium is reached between the solution concentration and the amount of coating, with or without pharmaceutical agent, deposited on the stent.

Brief Summary Paragraph Right (4):
We have discovered a process for coating stents that avoids bridging and allows for preferential coating of stent surfaces. The process comprises contacting a stent having a first and second surface with passages there between with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent while maintaining a fluid flow through said passages sufficient to prevent the film forming biocompatible polymer from substantially blocking said passages.

Brief Summary Paragraph Right (5):
In a preferred embodiment of the present invention the coating process would comprise placing a tubular stent having a first and second surface with passages there between on a mandrel and contacting the stent and mandrel with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent while moving the stent relative to the mandrel to cause fluid flow through said passages sufficient to prevent the film forming biocompatible polymer from substantially blocking said passages.

Brief Summary Paragraph Right (6):
In another embodiment of the present invention there is provided a coated stent, comprising a tubular stent having a first and second surface with passages there between, coated with a film-forming biocompatible polymer wherein the polymer coating is greater than 0.5 percent by weight of the coated stent and the passages are not substantially blocked by the bridging of the polymer coating.

Drawing Description Paragraph Right (1):
FIG. 1 illustrates a perspective view of a stent prior to coating.

Drawing Description Paragraph Right (2):
FIG. 2 is a perspective view that illustrates the placement of a stent on a mandrel prior to coating.

Drawing Description Paragraph Right (3):
FIG. 3 illustrates the movement of the stent relative to the mandrel in the after removal from the coating bath during the coating process.

Drawing Description Paragraph Right (4):
FIG. 4 is an enlarged view of a portion of the coated stent that illustrates the substantial absence of bridging of the stent slots or passages.

Drawing Description Paragraph Right (5):
FIG. 5 is a pictomicrograph that illustrates a stent that has been coated by conventional dip coating process with about a 4 weight percent coating solution.

Drawing Description Paragraph Right (6):
FIG. 6 is a pictomicrograph that illustrate a stent that has been coated by the inventive coating process with about a 13 weight percent coating solution.

Drawing Description Paragraph Right (7):
FIG. 7 is a graphical illustration of the in vitro release profile of a coated stent.

Drawing Description Paragraph Right (8):
FIG. 8 is a graphical illustration of the in vivo release profile of a coated stent.

Detailed Description Paragraph Right (1):
The present invention provides a process for coating medical devices. The process described herein is well suited to coating medical devices that have passages that may otherwise be blocked or have bridges formed by conventional dip coating. As previously discussed avoiding the formation of bridges is especially important in the coating of perforated structures such as stents. Bridging is a significant problem with stents with passages with a minor dimension less than about 125 mils, especially with passages having a minor dimension smaller than about 50 mils.

Detailed Description Paragraph Right (2):
Stents are generally cylindrical and perforated with passages that are slots, ovoid, circular or the like shape. Stents may also be composed of helically wound or serpentine wire structures in which the spaces between the wires form the passages. Stents may be flat perforated structures that are subsequently rolled to form tubular structures or cylindrical structures that are woven, wrapped, drilled, etched or cut to form passages. Examples of stents that may be advantageously coated by the present process include but are not limited stents described in the following U.S. Pat. Nos. 4,733,665 (hereinafter the Palmaz stent which is illustrated in FIG. 1); 4,800,882 (hereinafter the Gianturco stent); 4,886,062 (hereinafter the Wiktor stent) and 5,514,154 (hereinafter the Guidant RX Multilink.TM. stent). These stents can be made of biocompatible materials including biostable and bioabsorbable materials. Suitable biocompatible metals include, but are not limited to, stainless steel, tantalum, titanium alloys (including nitinol), and cobalt alloys (including cobalt-chromium-nickel alloys). Suitable nonmetallic biocompatible materials include, but are not limited to, polyamides, polyolefins (i.e. polypropylene, polyethylene etc.), nonabsorbable polyesters (i.e. polyethylene terephthalate), and bioabsorbable aliphatic polyesters (i.e. homopolymers and copolymers of lactic acid, glycolic acid, lactide, glycolide, para-dioxanone, trimethylene carbonate, .epsilon.-caprolactone, etc. and blends thereof).

Detailed Description Paragraph Right (3):
The present invention utilizes fluid flow or movement through the passages in the perforated medical device to avoid the formation of blockages or bridges. The fluid flow can be provided by active flow systems such as a perforated manifold inserted in the stent to circulate the coating fluid through the passages or can be created by placing the stent on a mandrel or in a small tube that is moved relative to the stent during the coating process to create sufficient fluid flow through the passages and thereby avoid the formation of blockages or bridges.

Detailed Description Paragraph Right (4):
In one embodiment of the present invention as illustrated in FIG. 2, a stent 2 is placed over a mandrel 6 that is smaller than the inner diameter d of the stent's intraluminal passage way 12 and dipped into the coating solution. The coated stent is moved relative to the mandrel after it is removed from the coating solution (preferably in one direction). FIG. 3 illustrates the movement of the stent 2 relative to the mandrel 6 after it is removed from bath. The relative outer diameter of the mandrel and inner diameter of the stent are such that after dipping, while the coating is still wet, the movement of the stent along the mandrel's length clears the passages (slots) which remain so on drying. The relative motion of the stent and mandrel, with limited clearance between the stent and mandrel, generates high shear rates which break the surface tension associated with the coating film filling the slots and provides smooth, defect free coating on the stent. Preferably the stent will be moved to an area of the mandrel that has not contacted the coating solution. As is illustrated in FIG. 3 that provides a perspective view of the stent 2 after being coated with coating 14. There are additional advantages: the coatings can be of high concentration and by proper choice of the mandrel diameter to stent diameter (the clearance), the relative thickness of the inner and outer coating of the stent can be controlled. For example, the stent coating can be thicker on the outer surface to contact the luminal wall or thicker on the interior surface to interact with the fluid stream.

Detailed Description Paragraph Right (5):
The mandrel may be of varying designs (i.e. tapered cones, cylindrical, slotted cylinders, mandrels having cross-sections that are ovoid, triangular or polygonal and would include shafts with veins or paddles). Additionally, the movement of the mandrel relative to the stent may not only be laterally, but may also consist of rotational movement. Object of the mandrel design being to assure sufficient shear flow relative to the passages to insure that the passages do not be come blocked.

Detailed Description Paragraph Right (6):
Film-forming polymers that can be used for coatings in this application can be absorbable or non-absorbable and must be biocompatible to minimize irritation to the vessel wall. The polymer may be either biostable or bioabsorbable depending on the desired rate of release or the desired degree of polymer stability, but a bioabsorbable polymer is preferred since, unlike biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Furthermore, bioabsorbable polymers do not present the risk that over extended periods of time there could be an adhesion loss between the stent and coating caused

by the stresses of the biological environment that could dislodge the coating and introduce further problems even after the stent is encapsulated in tissue.

Detailed Description Paragraph Right (8):
Suitable film-forming biostable polymers with relatively low chronic tissue response, such as polyurethanes, silicones, poly(meth)acrylates, polyesters, polyalkyl oxides (polyethylene oxide), polyvinyl alcohols, polyethylene glycols and polyvinyl pyrrolidone, as well as, hydrogels such as those formed from crosslinked polyvinyl pyrrolidinone and polyesters could also be used. Other polymers could also be used if they can be dissolved, cured or polymerized on the stent. These include polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers (including methacrylate) and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics such as polystyrene; polyvinyl esters such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as etheylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins and ethylene-vinyl acetate copolymers; polyamides,such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate, cellulose, cellulose acetate, cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers (i.e. carboxymethyl cellulose and hydoxyalkyl celluloses); and combinations thereof. Polyamides for the purpose of this application would also include polyamides of the form --NH--(CH.sub.2).sub.n --CO-- and NH--(CH.sub.2).sub.x --NH--CO--(CH.sub.2).sub.y --CO, wherein n is preferably an integer in from 6 to 13; x is an integer in the range of form 6 to 12; and y is an integer in the range of from 4 to 16. The list provided above is illustrative but not limiting.

Detailed Description Paragraph Right (9):
The polymers used for coatings must be film-forming polymers that have molecular weight high enough as to not be waxy or tacky. The polymers also must adhere to the stent and not be so readily deformable after deposition on the stent as to be able to be displaced by hemodynamic stresses. The polymers molecular weight be high enough to provide sufficient toughness so that the polymers will not to be rubbed off during handling or deployment of the stent and must not crack during expansion of the stent. The melting point of the polymer used in the present invention should have a melting temperature above 40.degree. C., preferably above about 45.degree. C., more preferably above 50.degree. C. and most preferably above 55.degree. C.

Detailed Description Paragraph Right (10):
The preferable coatings to use for this application are bioabsorbable elastomers, more preferably aliphatic polyester elastomers. In the proper proportions aliphatic polyester copolymers are elastomers. Elastomers present the advantage that they tend to adhere well to the metal stents and can withstand significant deformation without cracking. The high elongation and good adhesion provide superior performance to other polymer coatings when the coated stent is expanded. Examples of suitable bioabsorbable elastomers are described in U.S. Pat. No. 5,468,253 hereby incorporated by reference. Preferably the bioabsorbable biocompatible elastomers based on aliphatic polyester, including but not limited to those selected from the group consisting of elastomeric copolymers of .epsilon.-caprolactone and glycolide (preferably having a mole ratio of .epsilon.-caprolactone to glycolide of from about 35:65 to about 65:35, more preferably 45:55 to 35:65) elastomeric copolymers of .epsilon.-caprolactone and lactide, including L-lactide, D-lactide blends thereof or lactic acid copolymers (preferably having a mole ratio of .epsilon.-caprolactone to lactide of from about 35:65 to about 90:10 and more preferably from about 35:65 to about 65:35 and most preferably from about 45:55 to 30:70 or from about 90:10 to about 80:20) elastomeric copolymers of p-dioxanone (1,4-dioxan-2-one) and lactide including L-lactide, D-lactide and lactic acid (preferably having a mole ratio of p-dioxanone to lactide of from about 40:60 to about 60:40) elastomeric copolymers of .epsilon.-caprolactone and p-dioxanone (preferably having a mole ratio of .epsilon.-caprolactone to p-dioxanone of from about 30:70 to about 70:30) elastomeric copolymers of p-dioxanone and trimethylene carbonate (preferably having a mole ratio of p-dioxanone to trimethylene carbonate of from about 30:70 to about 70:30), elastomeric copolymers of trimethylene carbonate and glycolide (preferably having a mole ratio of trimethylene carbonate to glycolide of from about 30:70 to about 70:30), elastomeric copolymer of trimethylene carbonate and lactide including L-lactide, D-lactide, blends thereof or lactic acid copolymers (preferably having a mole ratio of trimethylene carbonate to lactide of from about 30:70 to about 70:30)

and blends thereof. As is well known in the art these aliphatic polyester copolymers have different hydrolysis rates, therefore, the choice of elastomer may in part be based on the requirements for the coatings adsorption. For example .epsilon.-caprolactone-co-glycolide copolymer (45:55 mole percent, respectively) films lose 90% of their initial strength after 2 weeks in simulated physiological buffer whereas the .epsilon.-caprolactone-co-lactide copolymers (40:60 mole percent, respectively) loses all of its strength between 12 and 16 weeks in the same buffer. Mixtures of the fast hydrolyzing and slow hydrolyzing polymers can be used to adjust the time of strength retention.

Detailed Description Paragraph Right (12):
The solvent is chosen such that there is the proper balance of viscosity, deposition level of the polymer, solubility of the pharmaceutical agent, wetting of the stent and evaporation rate of the solvent to properly coat the stents. In the preferred embodiment, the solvent is chosen such the pharmaceutical agent and the polymer are both soluble in the solvent. In some cases, the solvent must be chosen such that the coating polymer is soluble in the solvent and such that pharmaceutical agent is dispersed in the polymer solution in the solvent. In that case the solvent chosen must be able to suspend small particles of the pharmaceutical agent without causing them to aggregate or agglomerate into collections of particles that would clog the slots of the stent when applied. Although the goal is to dry the solvent completely from the coating during processing, it is a great advantage for the solvent to be non-toxic, non-carcinogenic and environmentally benign. Mixed solvent systems can also be used to control viscosity and evaporation rates. In all cases, the solvent must not react with or inactivate the pharmaceutical agent or react with the coating polymer. Preferred solvents include by are not limited to: acetone, N-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), toluene, methylene chloride, chloroform, 1,1,2-trichloroethane (TCE), various freons, dioxane, ethyl acetate, tetrahydrofuran (THF), dimethylformamide (DMF), and dimethylacetamide (DMAC).

Detailed Description Paragraph Right (13):
The film-forming biocompatible polymer coatings are generally applied to reduce local turbulence in blood flow through the stent, as well as, adverse tissue reactions. The coating may also be used to administer a pharmaceutically active material to the site of the stents placement. Generally, the amount of polymer coating to be placed on the stent will vary with the polymer and the stent design and the desired effect of the coating. As a guideline the amount of coating may range from about 0.5 to about 20 as a percent of the total weight of the stent after coating and preferably will range from about 1 to about 15 percent. The polymer coatings may be applied in one or more coating steps depending on the amount of polymer to be applied. Different polymers may also be used for different layers in the stent coating. In fact it is highly advantageous to use a dilute first coating solution as primer to promote adhesion of a subsequent coating layers that may contain pharmaceutically active materials.

Detailed Description Paragraph Right (14):
Additionally, a top coating can be applied to delay release of the pharmaceutical agent, or they could be used as the matrix for the delivery of a different pharmaceutically active material. The amount of top coatings on the stent may vary, but will generally be less than about 2000 .mu.g, preferably the amount of top coating will be in the range of about 10 .mu.g to about 1700 .mu.g and most preferably in the range of from about 300 .mu.g to about 1600 .mu.g. Layering of coating of fast and slow hydrolyzing copolymers can be used to stage release of the drug or to control release of different agents placed in different layers. Polymer blends may also be used to control the release rate of different agents or to provide desirable balance of coating (i.e. elasticity, toughness etc.) and drug delivery characteristics (release profile). Polymers with different solubilities in solvents can be used to build up different polymer layers that may be used to deliver different drugs or control the release profile of a drug. For example since .epsilon.-caprolactone-co-lactide elastomers are soluble in ethyl acetate and .epsilon.-caprolactone-co-glycolide elastomers are not soluble in ethyl acetate. A first layer of .epsilon.-caprolactone-co-glycolide elastomer containing a drug can be over coated with .epsilon.-caprolactone-co-glycolide elastomer using a coating solution made with ethyl acetate as the solvent. Additionally, different monomer ratios within a copolymer, polymer structure or molecular weights may result in different solubilities. For example, 45/55 .epsilon.-caprolactone-co-glycolide at room temperature is soluble in acetone whereas a similar molecular weight copolymer of 35/65 .epsilon.-caprolactone-co-glycolide is substantially insoluble within a 4 weight percent solution. The second coating (or multiple additional coatings) can be

used as a top coating to delay the drug deliver of the drug contained in the first layer. Alternatively, the second layer could contain a different drug to provide for sequential drug delivery. Multiple layers of different drugs could be provided by alternating layers of first one polymer then the other. As will be readily appreciated by those skilled in the art numerous layering approaches can be used to provide the desired drug delivery.

Detailed Description Paragraph Right (15):
The coatings can be used to deliver therapeutic and pharmaceutic agents such as, but not limited to: antiproliferative/antimitotic agents including natural products such as vinca alkaloids (i.e. vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (i.e. etoposide, teniposide), antibiotics (dactinomycin (actinomycin D) daunorubicin, doxorubicin and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin, enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which don't have the capacity to synthesize their own asparagine); antiproliferative/antimitotic alkylating agents such as nitrogen mustards(mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nirtosoureas (carmustine (BCNU) and analogs, streptozocin),trazenes-dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs (fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine{cladribine}); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (i.e. estrogen); Anticoaglants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase); antiplatelet: (aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab); antimigratory; antisecretory (breveldin); antiinflammatory: such as adrenocortical steroids (cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6.alpha.-methylprednisolone, triamcinolone, betamethasone, and dexamethasone), non-steroidal agents (salicylic acid derivatives i.e. aspirin; para-aminophenol derivatives i.e. acetominophen; Indole and indene acetic acids (indomethacin, sulindac, and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate); immunosuppressive: (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); Angiogenic: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF); nitric oxide donors; anti-sense olgio nucleotides and combinations thereof.

Detailed Description Paragraph Right (16):
Coating may be formulated by mixing one or more therapeutic agents with the coating polymers in a coating mixture. The therapeutic agent may be present as a liquid, a finely divided solid, or any other appropriate physical form. Optionally, the mixture may include one or more additives, e.g., nontoxic auxiliary substances such as diluents, carriers, excipients, stabilizers or the like. Other suitable additives may be formulated with the polymer and pharmaceutically active agent or compound. For example hydrophilic polymers selected from the previously described lists of biocompatible film forming polymers may be added to a biocompatible hydrophobic coating to modify the release profile (or a hydrophobic polymer may be added to a hydrophilic coating to modify the release profile). One example would be adding a hydrophilic polymer selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyethylene glycol, carboxylmethyl cellulose, hydroxymethyl cellulose and combination thereof to an aliphatic polyester coating to modify the release profile. Appropriate relative amounts can be determined by monitoring the in vitro and/or in vivo release profiles for the therapeutic agents.

Detailed Description Paragraph Right (17):
The best conditions for the coating application are when the polymer and pharmaceutic agent have a common solvent. This provides a wet coating that is a true solution. Less desirable, yet still usable are coatings that contain the pharmaceutic as a solid dispersion in a solution of the polymer in solvent. Under the dispersion conditions, care must be taken to ensure that the particle size of the dispersed pharmaceutical powder, both the primary powder size and its aggregates and agglomerates, is small enough not to cause an irregular coating surface or to clog the slots of the stent that we need to keep coating-free. In cases where a

dispersion is applied to the stent and we want to improve the smoothness of the coating surface or ensure that all particles of the drug are fully encapsulated in the polymer, or in cases where we may want to slow the release rate of the drug, deposited either from dispersion or solution, we can apply a clear (polymer only) top coat of the same polymer used to provide sustained release of the drug or another polymer that further restricts the diffusion of the drug out of the coating. The top coat can be applied by dip coating with mandrel as previously described or by spray coating (loss of coating during spray application is less problematic for the clear topcoat since the costly drug is not included). Dip coating of the top coat can be problematic if the drug is more soluble in the coating solvent than the polymer and the clear coating redissolves previously deposited drug. The time spent in the dip bath may need to be limited so that the drug is not extracted out into the drug-free bath. Drying should be rapid so that the previously deposited drug does not completely diffuse into the topcoat.

Detailed Description Paragraph Right (18):
The amount of therapeutic agent will be dependent upon the particular drug employed and medical condition being treated. Typically, the amount of drug represents about 0.001% to about 70%, more typically about 0.001% to about 60%, most typically about 0.001% to about 45% by weight of the coating.

Detailed Description Paragraph Right (19):
The quantity and type of polymers employed in the coating layer containing the pharmaceutic agent will vary depending on the release profile desired and the amount of drug employed. The product may contain blends of the same or different polymers having different molecular weights to provide the desired release profile or consistency to a given formulation.

Detailed Description Paragraph Right (21):
Individual formulations of drugs and polymers may be tested in appropriate in vitro and in vivo models to achieve the desired drug release profiles. For example, a drug could be formulated with a polymer (or blend) coated on a stent and placed in an agitated or circulating fluid system (such as PBS 4% bovine albumin). Samples of the circulating fluid could be taken to determine the release profile (such as by HPLC). The release of a pharmaceutical compound from a stent coating into the interior wall of a lumen could be modeled in appropriate porcine system. The drug release profile could then be monitored by appropriate means such as, by taking samples at specific times and assaying the samples for drug concentration (using HPLC to detect drug concentration). Thrombus formation can be modeled in animal models using the .sup.111 In-platelet imaging methods described by Hanson and Harker, Proc. Natl. Acad. Sci. USA 85:3184-3188 (1988). Following this or similar procedures, those skilled in the art will be able to formulate a variety of stent coating formulations.

Detailed Description Paragraph Right (22):
An absorbable elastomer based on 45:55 mole percent copolymer of .epsilon.-caprolactone and glycolide, with an IV of 1.58 (0.1 g/dl in hexafluoroisopropanol[HFIP] at 25.degree. C.) was dissolved five percent (5%) by weight in acetone and separately fifteen percent (15%) by weight in 1,1,2-trichloroethane. The synthesis of the elastomer is described in U.S. Pat. No. 5,468,253 incorporated herein by reference. Gentle heating can be used to increase the dissolution rate. The high concentration coating could be formulated with or without pharmaceutical agent present. An initial primer coat of only the polymer is put on Cordis P-S 153 stent (commercially available from Cordis, a Johnson & Johnson Company) by dip coating in the five percent (5%) solution while the stent is placed on a 0.032 inch (0.81 mm) diameter mandrel. The mandrel, with the stent on it, is removed from the dip bath and before the coating has a chance to dry the stent is moved along the length on the mandrel in one direction. This wiping motion applies high shear to the coating trapped between the stent and the mandrel. The high shear rate forces the coating out through the slots cut into the tube from which the stent is formed. This wiping action serves to force the coating out of the slots and keeps them clear. The "primed stent" is allowed to air dry at room temperature. The prime coat is about 100 micrograms of coating. After 1-2 hours of air drying, the stent is remounted on a 0.0355 inch (0.9 mm) clean mandrel and dipped into a second, concentrated coat solution. This can be drug free or can contain about six percent (6%) by weight drug in addition to about fifteen percent (15%) polymer by weight in the coating solution. The dip and wipe process is repeated. The final coated stent is air dried for 12 hours and then put in a 60.degree. C. vacuum oven (at 30 in Hg vacuum) for 24 hours to dry. This method provides a coated stent with about 270

micrograms of polymer and about 180 micrograms of drug.

Detailed Description Paragraph Right (23):
This example describes experiments that demonstrate the ability of the dip and wipe coating approach to incorporate a bioactive agent in the coating and that the bioactive agent retains its biological activity. An initial primer coat of only the polymer described in Example 1 was placed on Cordis P-S 153 stent by dip coating in the five percent (5%) solution by weight while the stent is placed on a 0.032 inch (0.81 mm) diameter mandrel. And primed as described in Example 1. The coated stent was then coated a second time with a coating solution of polymer and drug. The coated stent was dipped and wipe coated using the mandrel and a high concentration drug-polymer (15% polymer, 1:100 drug:polymer, and 2000 U/ml heparin-benzalkonium chloride [HBAC]; all in 70/30 acetone/DMSO) solution by the method described in Example 1. The HBAC coated stents had a total coating weight of about 350 micrograms. Coated stents were sent to North American Science Assocites Inc. (Northwood, Ohio U.S.A.) for a standard rabbit whole blood clotting time assay. The assay was performed by placing the stents on the surface of the Tryptic Soy Agar (TSA) plate along with a negative control sample (glass tubing) and a positive control (HBAC coated glass tubing). The 15.times.150 mm TSA plate was flooded with 35 ml of whole rabbit blood, obtained by arterial draw of a euthanized rabbit. The test plate was incubated in ambient room temp. For 20-40 minutes. Following the incubation period, the samples were removed from the thrombus formed in the plate using forceps. The test and control sections were observed for evidence of adherence to the thrombus formation upon removal.

Detailed Description Paragraph Right (24):
The heparinized stents were proven to be nonthrombogenic as compared with the non-heparinized controls.

Detailed Description Paragraph Right (25):
This example describes experiments that demonstrate the ability of the dip and wipe coating approach to provide coated stent with high coating loading and no bridging of the slots in the stent. A Cordis P-S 153 stent was taken and dip coated into a five percent (5%) solution of the elastomeric 45:55 mole percent of .epsilon.-caprolactone and glycolide copolymer (IV=1.58) described in Example 1. The stent was removed and allow to air dry for 1-2 hours at room temperature. The coating added to the stent was about 100-150 micrograms. The slots in the stent were bridged with dry coating film (FIG. 5). A second Cordis P-S 153 was dipped and wipe coated with the coating solution containing fifteen percent (15%) polymer as described in Example 1. The stent was found to have slots free of coating and to be loaded with 300 micrograms of coating. Similar experiments were performed with the Cordis Crown.TM. stent, the Guidant RX Multilink.TM. stent and the AVE GFX .TM.stent. The results were identical, dipping and wipping over a mandril allows high concentration coatings to provide high coating build on a variety of stents without the adverse effect of bridging the slots.

Detailed Description Paragraph Right (26):
This example demonstrates the differential solubility of elastomeric .epsilon.-caprolactone and glycolide copolymers and elastomeric .epsilon.-caprolactone and lactide copolymers in ethyl acetate. 0.2 g of .epsilon.-caprolactone and glycolide copolymer (45/55, IV=1.5, Tm .about.62.degree. C.) were placed in a flat bottom glass vial along with 4 grams of ethyl acetate. These were heated to about 50.degree. C. on a hot plate with stirring bar over night. The result was partial solution with clear polymer on the walls and a cloudy solution at 50.degree. C. but the polymer precipitated out and coated the walls of the vial when the temperature came back to room temperature (.about.25.degree. C). Similarly, 0.2 g of .epsilon.-caprolactone and lactide copolymer (40/60, IV=1.5, Tm .about.132.degree. C.) were placed in a flat bottom glass vial with 4 g of ethyl acetate made in a manner similar to that described in Example 11. These were heated to about 50.degree. C. on a hot plate with stirring bar over night. The particles first swelled and then went into solution. On cooling to room temperature the solution remained clear and uniform.

Detailed Description Paragraph Right (27):
P-S stents were coated from a 5% w/w 45:55 .epsilon.-caprolactone and glycolide solution as described in the example 1. The initial coating resulted in .about.100 micrograms of total solid on the stent. The stents were dried and then coated from a 15% w/w 45:55 .epsilon.-caprolactone and glycolide and 6% w/w drug solution. The second step resulted in .about.170 micrograms of total solid and .about.60

micrograms of drug on the stent. Stents were coated again from the same second solution and an increment of 30 micrograms (a total of 200 micrograms) of total solid and an increment of 20 micrograms of drug (a total of 80 micrograms) was observed. However when the dried stents were coated again with the same second solution total weight gain of the solid and the drug remain same.

Detailed Description Paragraph Right (28):
This Example describes applying a top coating to a coated stent with an ultrasonic spraying device.

Detailed Description Paragraph Right (29):
A five percent by weight coating solution is made using 45:55 .epsilon.-caprolactone and glycolide described in Example 1 in a solvent solution of TCE:Acetone (1:1, w/w)

Detailed Description Paragraph Right (30):
The ultrasonic spray unit is composed of a SonoTek (New York, U.S.A.) broadband ultrasonic generator (model 60-05108) attached to a nozzle (model 06-04010) an oscillated at 60 KHz to generate a mean droplet size of 31 microns. The power at which the system was operated was is 5.8 mWatts. The flow rate was adjusted to about 0.3 ml/min. The ultrasonic spray system was placed in a plastic bag containment system to eliminate air currents and to slow evaporation. Stents would be positioned 1.5-5 cm distance from the nozzle and had a dwell time in the spray cloud of about 15-40 seconds.

Detailed Description Paragraph Right (31):
The stent would then be dried in ambient conditions for 18-24 hours and subsequently vacuum dried at 60.degree. C. for 24 hours. Approximately, 100-150 micrograms of polymer was deposited per top coating run. A mandrel can be used to prevent coating the inside of the stent if desired.

Detailed Description Paragraph Right (32):
This Example describes the preparation of coated stents containing various levels of rapamycin for in vitro drug release testing.

Detailed Description Paragraph Right (33):
0.06 gms of Rapamycin was dissolved into 0.8 gms of 15% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1 and the coated stents were designated as `Std 33%`.

Detailed Description Paragraph Right (34):
0.015 gms of Rapamycin was dissolved into 0.5 gms of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 14.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1 and the coated stents were designated as `14%`

Detailed Description Paragraph Right (35):
0.028 gms of rapamycin was dissolved into 0.5 gm of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated with polymer-only solution as described in Example 6. The final coated stents were designated as `24-TC%`

Detailed Description Paragraph Right (36):
0.028 gms of rapamycin was dissolved into 0.5 gm of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated with polymer-only solution as described in Example 6;

Detailed Description Paragraph Right (37):
However, a total volume of 200 microliters of spray solution was used in this case. The final coated stents were designated as `24-Thick TC%`

Detailed Description Paragraph Right (38):
0.06 gms of rapamycin was dissolved into 0.8 gm of 15% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated twice with .epsilon.-caprolactone-co-lactide (Cap/Lac)

solution as described in Example 4. The final coated stents were designated as `33-TC%`.

Detailed Description Paragraph Right (39):
0.06 gms of rapamycin was dissolved into 0.8 gm of 15% CAP/LAC solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in example 1. The dip-coated stents were spray coated twice with polymer-only solution as described in Example 6 (except .epsilon.-caprolactone-co-lactide was used as the copolymer). The final coated stents were designated as `33-C/L TC%`.

Detailed Description Paragraph Right (40):
This example describes the results of testing the in vitro drug release of rapamycin from coated stent.

Detailed Description Paragraph Right (41):
Coated stents were prepared as described in Example 7 with varying concentrations of rapamycin were tested for the in vitro release of rapamycin into an aqueous ethanol solution. As is indicated in FIG. 7, the stents denoted by the diamonds had a primer coating and a base coating that contained rapamycin. The total weight of the coating and rapamycin on the each stent was approximately 450 .mu.g and contained 33 percent by weight of rapamycin. The coating was a copolymer of .epsilon.-caprolactone-co-glycolide (45:55 mole percent) applied by dip coating. The squares represent data points for stents having a primer coating and a base coating containing rapamycin. The total weight of the coating and drug was approximately 450 .mu.g, which contained 14 percent by weight rapamycin. The coating material was also a copolymer of .epsilon.-caprolactone-co-glycolide (45:55 mole percent) applied by dip coating. The triangles represent data points for stents that had a primer coating and a base coating containing rapamycin. A primer coating and base coating (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stent. A top coat of 200 .mu.g (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was 650-700 .mu.g, which contained 24 percent by weight rapamycin. The Xs represent data points for stents that had a primer coat and a base coating containing rapamycin. The primer coating and base coating (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stent. A top coat of 100 .mu.g (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was 550-600 .mu.g, which contained 24 percent by weight rapamycin. The asterisk represents data points for stents that was coated with a primer, a base coat and two top coats. The primer coating and base coating (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stents. A top coat of 100 .mu.g (.epsilon.-caprolactone-co-glycolide; 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was approximately 550 .mu.g, which contained 33 percent by weight rapamycin. The circles represent data points for stents that were dip coated with .epsilon.-caprolactone-co-lactide (40:60 mole percent). The stents were then top coated with an ultrasonic spray with approximately 100 .mu.g of .epsilon.-caprolactone-co-lactide. The total coating weighed about 550 .mu.g and contained 33 percent by weight rapamycin.

Detailed Description Paragraph Right (42):
Each stent was placed in a 2.5 mL of release medium (aqueous ethanol; 15 percent by volume at room temperature) contained in a 13.times.100 mm culture tube. The tube was shaken in a water bath (INNOVA.TM. 3100; New Brunswick Scientific) at 200 rpm while maintaining ambient conditions. After a given time interval (ranging from 15 minutes to one day) the tubes were removed from the shaker and the respective stents carefully transferred to a fresh 2.5 ml Aliquot of release medium. The new tube was placed on the shaker and agitation resumed. A sample was removed from the aliquot, which had previously contained the stent and placed in a HPLC vial for determination of the rapamycin content by HPLC.

Detailed Description Paragraph Right (43):
The HPLC system used to analyze the samples was a Waters Alliance with a PDA 996. This system is equipped with a photodiode array detector. 20 .mu.L of each sample was withdrawn and analyzed on a C.sub.18 -reverse phase column (Waters Symmetry.TM. Column: 4.6 mm.times.100 mm RP.sub.18 3.5 .mu.m with a matching guard column) using a mobile phase consisting of acetonitrile/methanol/water (38:34:28 v/v) delivered at a flow rate of 1.2 mL/min. The column was maintained at 60.degree. C. through the

analysis. Under these analytical conditions rapamycin had a retention time of 4.75.+-.0.1 minutes. The concentration was determined from a standard curve of concentration versus response (area-under the curve) generated from rapamycin standards in the range of from 50 ng/mL to 50 .mu.g/mL.

Detailed Description Paragraph Right (44):
The results from testing the coated stents described above is shown in FIG. 7.

Detailed Description Paragraph Right (45):
The goal of this study was to assess the rate of release of rapamycin from polymer-coated stents introduced in vivo into the coronary arteries of Yorkshire pigs. At various times after introduction of stents, the pigs were euthanized and the coronary arteries removed, the stents dissected free of the artery and analysed for rapamycin content using loading assay previously described. Through comparison with the amount of rapamycin contained on control, non-implanted stents, the in vivo rate of rapamycin release from the polymer coatings could be determined.

Detailed Description Paragraph Right (47):
To minimize the chance for clot formation at the stent site, animals were started on oral aspirin 325 mg per day three days prior to the planned procedure. Upon confirmation of adequate depth of anesthesia, the right inguinal region was shaved and sterilized, and sterilely draped. Aseptic technique was used throughout the remainder of the procedure. A linear incision parallel to the femoral vessels was made and the subcutaneous tissues dissected to the level of the artery. After adequate exposure, the femoral artery was isolated proximally with umbilical tape and distally with a 3.0 silk tie for hemostasis. Using surgical scissors, an arteriotomy was made, and an 8 Fr sheath inserted in the artery. Heparin 4,000 units and bretylium 75 mg were then administered intravenously after sheath insertion. Electrocardiogram, respiratory pattern, and hemodynamics were continuously monitored.

Detailed Description Paragraph Right (48):
A hockey stick guiding catheter was inserted via the femoral sheath, and advanced to the left coronary ostium, whereupon left coronary cineangiography was performed. A single frame anteroposterior radiogram was developed, and the luminal diameters of the left anterior descending and circumflex arteries measured, in order to size the balloon-stent assembly for a prespecified balloon-to-artery ratio of approximately 1.1-1.2:1. Using guide catheter support and fluoroscopic guidance, a 0.014" guidewire was advanced into the lumen of the left anterior descending artery. Intracoronary stenting was performed by advancing a stent mounted on a conventional angioplasty balloon into position in the mid-portion of the left anterior descending artery. The stent was deployed by inflating the mounting balloon to 8 atmospheres for 30 seconds. Upon confirmation of vessel patency, the balloon and guidewire were removed from the left anterior descending artery, and the identical procedure was performed in the left circumflex artery. Upon completion of stent delivery in the left circumflex artery, the balloon and guidewire were withdrawn.

Detailed Description Paragraph Right (50):
At various times after stent implantation, euthanasia was performed by overdose of pentobarbital administered IV. The chest was opened via a mid-sternal incision and the heart removed. Both the LAD and LCX were carefully dissected free of surrounding tissue. The stent was then dissected free of the arterial tissue and placed in a vial. The arterial tissue was frozen and stored for later analysis by HPLC.

Detailed Description Paragraph Right (51):
FIG. 7 illustrates a typical in vivo release curve for a stent coating consisting of 33% rapamycin in polycaprolactone-co-glycolide.

Detailed Description Paragraph Right (52):
This Example describes the in vivo testing of coated stents in a porcine coronary artery model.

Detailed Description Paragraph Right (53):
This preliminary study was conducted to assess the ability of rapamycin released from .epsilon.-caprolactone-co-glycolide copolymer-coated stents to inhibit intimal hyperplasia in vivo. Fourteen days after receiving rapamycin-loaded or control polymer coated stents, the male Yorkshire pigs were euthanized and the coronary arteries removed, the vessels prepared for histological evaluation and analysed for the amount of intimal growth. Through comparison control metal stents and stents

containing polymer only, the in vivo ability of rapamycin to prevent neointimal growth could be determined.

Detailed Description Paragraph Right (54):
Ethylene oxide-sterilized Palmaz-Schatz stents were implanted under sterile conditions in anesthetized farm pigs weighing 38 to 48 kg. Twenty-four hours prior to stent implantation, animals were given aspirin (325 mg, p.o., qd) and ticlopidine (250 mg, p.o., qd) to control chronic thrombosis; both aspirin and ticlopidine were continued daily until sacrifice. Anesthesia was induced with ketamine (20 mg/kg, i.m.), xylazine (2 mg/kg, i.m.) and sodium pentobarbital (10 mg/kg as needed) and maintained on 1-2% isofluorane in oxygen. An 8 Fr sheath was placed in an asceptically isolated left carotid artery and used subsequently to conduct either an 8 Fr JL 3.5 guide catheter for coronary angiography or to place a 0.014 inch guidewire for balloon delivery of stents to the appropriate coronary arteries. Heparin (150 unit/kg) was administered intraprocedurally to prevent acute thrombosis. Four experimental groups were employed; 1) metal stent control; 2) metal stent coated with 45/55 (w/w) .epsilon.-caprolactone glycolide copolymer (CAP/GLY); 3) 32 .mu.g rapamycin/stent formulated in CAP/GLY; 4) 166 .mu.g rapamycin/stent formulated in CAP/GLY. Stents were deployed in both the LAD and LCX coronary arteries. Angiography was performed prior to, during, and immediately after stenting to both size the vessel for choice of balloon diameter (3.0, 3.5 or 4.0 mm) and to obtain measurements for determination of the balloon/artery ratio. Stents were deployed by inflating the delivery balloon to 8-10 ATM for 30 sec. Angiography was also performed at 14 days post-implantation to obtain final vessel diameter. Treatment groups were randomized and individual stents were implanted by an investigator who was blinded as to the treatment. However, only one treatment was employed in any given pig. Fourteen days after implantation, animals were killed, the vessels were perfusion fixed for 10 minutes at 100 mmHg with 10% formalin and then stored in 10% buffered formalin.

Detailed Description Paragraph Right (55):
For histological assessment, the stented vessel was embedded in glycol methacrylate. Four 3-5 .mu.m thick cross-sections taken at equal intervals along the length of the stent were placed on glass slides and prepared with Miller's Elastin stain. Histomorphometric measurements were determined in each section via microscopy and computerized image analysis. Individual values obtained for each vessel represent the average of the 4 measured sections. Differences between treatments were assessed by ANOVA and Dunnett's test.

Detailed Description Paragraph Right (56):
As can be seen in Table 1, local delivery of rapamycin to injured coronary arteries resulted in a significant ($p<0.05$) reduction in intima:media ratio in the 166 .mu.g treatment group and a small but non-significant reduction in the 32 .mu.g treatment group when compared with the polymer and bare metal control groups. Rapamycin delivered from the GAP/GLY coating also resulted in non-significant dose-related decreases in neointimal area in both the 32 .mu.g and 166 .mu.g treatment groups. The percent diameter stenosis as assessed by angiography was also significantly reduced in the 2 rapamycin treatment groups when compared to the CAP/GLY group, although the reduction in this parameter from the metal control was small and non-significant. Never-the-less, in this preliminary 14 day study, these data suggest that local release of rapamycin from a biodegradable hydrophobic polymer coating may be capable of limiting the amount of neointimal proliferation which occurs as a result of stent deployment.

Detailed Description Paragraph Table (1):
TABLE 1 Histology Angiography Intima/ Intimal % Diameter B/A Treatment Media ratio Area (mm.sup.2) Stenosis Ratio

Metal Control 0.90 .+-. 3.65 .+-. 24.8 .+-. 3.9.sup.1 1.27 .+-. (n = 10) 0.05 0.82 0.05
CAP/GLY (n = 8) 0.91 .+-. 4.15 .+-. 38.0 .+-. 4.0 1.32 .+-. 0.11 0.23 0.04
CAP/GLY + 32 .mu.g 0.75 .+-. 3.27 .+-. 21.6 .+-. 3.6.sup.1 1.23 .+-. rapamycin (n = 10) 0.04 0.16 0.03
CAP/GLY + 166 .mu.g 0.65 .+-. 2.87 .+-. 23.9 .+-. 2.3.sup.1 1.27 .+-. rapamycin (n = 8) 0.04.sup.1,2 0.31 0.05

.sup.1 p < 0.05 from CAP/GLY .sup.2 p < 0.05 from Metal Control All values are mean .+-. sem. B/A ratio = balloon to artery ratio, an index of the consistency of stent expansion from group to group

CLAIMS:

1. A method for coating a stent having an outer surface and inner surface with

passages between the outer surface and inner surfaces comprising:

(a) contacting the stent with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent;

(b) before the coating solution dries creating fluid movement out of the passages of the stent sufficient to prevent the film forming biocompatible polymers from substantially blocking said passages thereafter;

(c) drying the stent to provide at least a partially coated stent with a first coating

wherein said fluid movement is created by contacting a mandrel with the inner surface of the stent and moving the mandrel relative to the stent to prevent bridges from forming in said passages.

2. The method of claim 1 wherein the stent is contacted with the coating solution by dipping the stent into the coating solution.

3. The method of claim 1 wherein the stent is contacted with the coating solution by spraying the coating solution on to the stent.

4. The method of claim 2 wherein fluid movement is created by contacting the outer surface of the stent with the inner surface of a tube and moving the tube relative to the stent to prevent bridges from forming in said passages.

5. The method of claim 3 wherein fluid movement is created by contacting the outer surface of the stent with the inner surface of a tube and moving the tube relative to the stent to prevent bridges from forming in said passages.

10. The method of claim 1 wherein additionally contained in the coating solution is a pharmaceutically active compound.

12. The method of claim 11 wherein the pharmaceutically active compound is rapamycin.

13. The method of claim 1 wherein after the stent is dried a second coating is applied.

14. The method of claim 13 wherein the second coating is applied by spraying a solution containing a film forming biocompatible polymer onto at least one surface of the stent.

15. The method of claim 13 wherein the second coating contains a film forming biocompatible polymer not present in the first coating.

16. A method for coating a tubular stent having a first surface and second surface with passages between the first surface and second surfaces comprising;

(a) placing the tubular stent on a mandrel; then

(b) contacting the stent and mandrel with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent while moving the stent relative to the mandrel to cause fluid flow through said passages sufficient to prevent the film forming biocompatible polymer from substantially blocking said passages; thereafter

(c) drying the stent to provide at least a partially coated tubular stent with a first coating.

18. The method of claim 16 wherein the stent is coated with an elastomeric aliphatic polyester.

21. The method of claim 20 wherein a second coating is applied.

22. The method of claim 21 wherein the first coating is .epsilon.-caprolactone-co-glycolide and the second coating is

.epsilon.-caprolactone-co-glycolide.

23. The method of claim 22 wherein the first coating contains a pharmaceutically active compound.

25. The method of claim 24 wherein a second coating is applied.

26. The method of claim 25 wherein the first coating is .epsilon.-caprolactone-co-lactide and the second coating is .epsilon.-caprolactone-co-lactide.

27. The method of claim 25 wherein the first coating is .epsilon.-caprolactone-co-lactide and the second coating is .epsilon.-caprolactone-co-glycolide.

28. The method of claim 26 wherein the first coating contains a pharmaceutically active compound.

29. The method of claim 27 wherein the first coating contains a pharmaceutically active compound.

30. The method of claim 26 wherein the pharmaceutically active compound is rapamycin.

31. The method of claim 27 wherein the pharmaceutically active compound is rapamycin.

34. The method of claim 25 wherein the second coating is a coating applied to modulate the release rate of the pharmaceutical agent in the first coating.

35. The method of claim 34 wherein the second coating weights between about 10 micrograms and about 2000 micrograms.

36. The method of claim 34 wherein the second coating weights between about 100 micrograms and about 1700 micrograms.

DOCUMENT-IDENTIFIER: US 6369039 B1
TITLE: High efficiency local drug delivery

Brief Summary Paragraph Right (3):
As an example of localized delivery of therapeutic agents, in vivo adenoviral gene transfer has been accomplished with the use of site-specific delivery catheters. Independent of the local delivery device used, most studies have delivered viral doses ranging from 1.times.10.sup.9 to 1.times.10.sup.10 pfu/ml over extended delivery times of 20 minutes or longer, and typically in delivery volumes of 1 ml or more. Although these conditions are widely used, the lack of optimization studies with local delivery devices suggests that delivery conditions are not necessarily optimal. Moreover, conventional localized techniques are often invasive in that they typically involve side branch ligation, long delivery times, and when the delivery device is an expandable device such as a balloon catheter, these techniques usually are associated with high pressures to accomplish drug delivery. Localized delivery techniques making use of long delivery times and high pressures and volumes often result in tissue damage, ischemia and other problems. Attempts have been made to reduce the delivery time from an infusion based device using a polymer carrier such as Poloxamer (BASF Corporation), whereby delivery times are reduced from 30 minutes to 5 minutes. The clinical utility of this approach, however, remains uncertain.

Drawing Description Paragraph Right (3):
FIG. 3 shows a stent used in accordance with an embodiment of the present invention.

Detailed Description Paragraph Right (1):
The present invention overcomes the deficiencies of conventional localized drug delivery techniques by providing a site-specific, minimally-invasive method of delivering therapeutic agents to tissue. The method of the present invention advantageously makes use of low delivery pressures and short delivery durations to provide for the quick and safe localized delivery of therapeutic agents to any suitable lumen, cavity, or tissue in the body such as, for example, blood vessels, heart tissue, and locations within the gastrointestinal tract and urological and gynecological systems. The terms "drug" and "therapeutic agent" are used interchangeably herein and include pharmaceutically active compounds, nucleic acids with and without carrier vectors such as lipids, compacting agents (such as histones), virus, polymers, proteins, and the like, with or without targeting sequences.

Detailed Description Paragraph Right (5):
To achieve high efficiency drug delivery by concentration-driven molecular diffusion, the therapeutic agent is incorporated into the medical device as a substantially saturated solution. As used herein, "substantially saturated solution" means that the concentration of dissolved therapeutic agent in a solvent, such as water or another physiologically acceptable carrier, is at least about 75%, preferably at least about 80%, 85%, 90%, 95% or 100% of the limit of solubility of the therapeutic agent in the solvent. Alternatively, the concentration of the therapeutic agent is limited by the concentration that results in an undesirable toxic response from a patient. The substantially saturated solution is "associated with" the medical device in that the therapeutic agent is held in a cavity(ies) of the device, such as in an infusion style catheter such as a channel balloon catheter; or the therapeutic agent is coated onto the surface of the device as a coating per se or as part of a coating; or the substantially saturated solution is held within or passes through the medical device, such as in a needle injection catheter.

Detailed Description Paragraph Right (6):
The present invention is described herein with specific reference to an expandable

catheter as the medical device. Other medical devices within the scope of the present invention include implantable devices such as needle injection catheters, hypodermic needles, stents, blood clot filters, vascular grafts, stent grafts, aneurysm filling coils, trans myocardial revascularization ("TMR") devices, percutaneous myocardial revascularization ("PMR") devices etc., as are known in the art.

Detailed Description Paragraph Right (7):
The catheter used with the present invention is any suitable catheter such as, for example, an infusion catheter (such as a channeled balloon catheter as described in U.S. Pat. No. 5,254,089, incorporated herein by reference, transport catheter, or microporous balloon catheter), an angioplasty balloon catheter, a double balloon catheter, or an infusing sleeve catheter, as are known in the art. The therapeutic agent is applied to, or is incorporated into, the expandable portion of such catheters. For example, the therapeutic agent is included as part of a polymer coating that is applied to said expandable portions. Alternatively, the therapeutic agent is incorporated directly into the expandable portion. Alternatively, the therapeutic agent is introduced into the catheter after the catheter is positioned to the target tissue by infusing the therapeutic agent through the infusion port of an-infusion catheter.

Detailed Description Paragraph Right (9):
With specific reference to FIG. 1, the delivery of a therapeutic agent to a target location is accomplished with the use of a medical device 100 comprising a catheter 110 having an expandable portion 120. The expandable portion 120 of the catheter 110 is optionally coated with a polymer for holding the therapeutic agent during delivery into the body. The polymer coating 130 is preferably capable of absorbing a substantial amount of drug solution. The polymer coating 130 is placed onto the expandable portion 120 by any suitable mean such as, for example, by immersion, spraying, or deposition by plasma or vapor deposition. The polymer is typically applied to a thickness of about 1 to 30 microns, preferably about 2 to 5 microns. Very thin polymer coatings, e.g., of about 0.2-0.3 microns and much thicker coatings, e.g., more than 30 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of polymer coating onto the expandable portion 120 of catheter 110. Such multiple layers can be of the same or different polymer materials, and may perform different functions (e.g., for biocompatibility, to control drug release, etc.).

Detailed Description Paragraph Right (10):
The polymer coating 130 comprises any polymeric material capable of absorbing or otherwise holding the therapeutic agent to be delivered. The polymeric material is, for example, hydrophilic, hydrophobic, and/or biodegradable, and is preferably selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyurethanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylatic acids, polyglycolic acids, polycaprolactones, polyhydroxybutyrate valerates, polyacrylamides, polyethers, and mixtures and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. Preferred polymers include polyacrylic acid as described in U.S. Pat. No. 5,091,205, the disclosure of which is incorporated herein by reference; and aqueous coating compositions comprising an aqueous dispersion or emulsion of a polymer having organic acid functional groups and a polyfunctional crosslinking agent having functional groups capable of reacting with organic acid groups, as described in U.S. Pat. No. 5,702,754, the disclosure of which is incorporated herein by reference.

Detailed Description Paragraph Right (11):
The therapeutic agent is introduced onto the expandable portion 120, or alternatively, into the polymer coating 130, by any suitable method. For example, the therapeutic agent is placed in solution, which is thereafter applied to the expandable portion 120 or polymer coating 130 by any suitable means, including dipping into the drug solution or applying the solution by pipet or spraying. In the former method, the amount of drug loading is controlled by regulating the time the polymer coating 130 is immersed in the drug solution, the extent of polymer coating cross-linking, the interactions between the polymer and drug (i.e., bonding, Van der Waals forces, charge interactions, etc.), the concentration of the drug in the solution and/or the amount of polymer coating 130. In another embodiment of the

invention, the drug is incorporated directly into the polymer used in the polymer coating 130 prior to the application of the polymer as a coating onto a medical device. When the medical device used in the present invention is an infusion catheter 400, such as that shown in cross-section in FIG. 2, the substantially saturated solution of therapeutic agent (shown in FIG. 2 as 405) is not coated onto the catheter, but rather is delivered to the target tissue by infusing through the channels 410 of the infusion catheter 400.

Detailed Description Paragraph Right (12):
The therapeutic agents used in the present invention include, for example, pharmaceutically active compounds, proteins, oligonucleotides, ribozymes, anti-sense genes, DNA compacting agents, gene/vector systems (i.e., anything that allows for the uptake and expression of nucleic acids), nucleic acids (including, for example, recombinant nucleic acids; naked DNA, cDNA, RNA; genomic DNA, CDNA or RNA in a non-infectious vector or in a viral vector which may have attached peptide targeting sequences; antisense nucleic acid (RNA or DNA); and DNA chimeras which include gene sequences and encoding for ferry proteins such as membrane translocating sequences ("MTS") and herpes simplex virus-1 ("VP22")), and viral, liposomes and cationic polymers that are selected from a number of types depending on the desired application. For example, biologically active solutes include anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, PPACK (dextrophenylalanine proline arginine chloromethylketone), rapamycin, probucol, and verapimil; angiogenic and anti-angiogenic agents; anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine; antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet factors; vascular cell growth promoters such as growth factors, growth factor receptor antagonists, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; agents which interfere with endogeneus vascoactive mechanisms; survival genes which protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; and combinations thereof. These and other compounds are added to the polymer coating using similar methods and routinely tested as set forth in the specification. Any modifications are routinely made by one skilled in the art.

Detailed Description Paragraph Right (13):
Polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell. Examples of therapeutic polynucleotides include anti-sense DNA and RNA; DNA coding for an anti-sense RNA; or DNA coding for tRNA or rRNA to replace defective or deficient endogenous molecules. The polynucleotides of the invention can also code for therapeutic polypeptides. A polypeptide is understood to be any translation product of a polynucleotide regardless of size, and whether glycosylated or not. Therapeutic polypeptides include as a primary example, those polypeptides that can compensate for defective or deficient species in an animal, or those that act through toxic effects to limit or remove harmful cells from the body. In addition, the polypeptides or proteins that can be incorporated into the polymer coating 130, or whose DNA can be incorporated, include without limitation, angiogenic factors including acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor .alpha. and .beta., platelet-derived enotheial growth factor, platelet-derived growth factor, tumor necrosis factor .alpha., hepatocyte growth factor and insulin like growth factor; growth factors; cell cycle inhibitors including CDK inhibitors; thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, including agents for treating malignancies; and combinations thereof. Still other useful factors, which can be provided as polypeptides or as DNA encoding these polypeptides, include monosite chemoattractant protein ("MCP-1"), and the family of

bone morphogenic proteins ("BMP's"). The known proteins include BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively or, in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them.

Detailed Description Paragraph Right (15):
After the therapeutic agent is incorporated into the inflatable portion 120 or coating 130, the medical device 100 is introduced into the body and positioned to a target location through a body cavity or vasculature (e.g., coronary arteries, portal vein, ileofemoral vein, etc.) by torquing or other known techniques. Once the medical device 100 is positioned to a target location within the body, the expandable portion 120 is optionally expanded and the drug is released at a pressure of not more than about 5 atmospheres, preferably not more than about 1 atmosphere, and more preferably, not more than about 0.1 atmosphere. The medical device 100 is held at the target location for a duration of not more than about 5 minutes, preferably not more than about 2 minutes, and more preferably not more than about 1 minute. After delivery, the medical device 100 is removed from the body by known techniques.

Detailed Description Paragraph Right (16):
In one embodiment, the medical device 100 of the present invention includes a stent 300 (FIG. 3) for placement in a body lumen. The present invention can thus be used for the dual purpose of localized drug delivery and stent placement. As known in the art, stents are tubular support structures that are implanted inside tubular organs, blood vessels or other tubular body lumens. The stent used with the present invention is of any suitable design, and is either self-expanding or balloon-expandable. The stent is made of any suitable metallic (e.g., stainless steel, nitinol, tantalum, etc.), polymeric (e.g., polyethylene terephthalate, polyacetal, polylactic acid, polyethylene oxide-polybutylene terephthalate copolymer, etc.) or biodegradable material. The stent 300 is preferably metallic and configured in a mesh design, as shown in FIG. 3. When used with the present invention, the stent 300 is placed over the expandable portion 120 of the catheter 110. The medical device 100 is thereafter delivered to a target location within the body. In this embodiment, the target location is situated within a body lumen. When the expandable portion 120 is expanded during the release of the drug agent from within the expandable portion 120 or the polymer coating 130, the stent 300 is likewise expanded. After the drug agent has been released from the expandable portion 120 or the polymer coating 130, the expandable portion 120 is compressed or deflated. The stent 300, however, remains in its expanded state within the body lumen.

Detailed Description Paragraph Right (17):
Referring to the embodiment of the invention illustrated in FIG. 4, the expandable portion 120 of the catheter 110 is optionally covered by a protective sheath 210 while the medical device 100 is inserted into the body and positioned at a target location within a body lumen 200. Such a sheath is particularly advantageous in the case of long arterial transit times (i.e., to position the catheter to the target location) or when the therapeutic agent to be delivered is highly toxic. As the expandable portion 120 is positioned at a target occluded site 220, the protective sheath 210 is drawn back to expose the expandable portion 120 and thus to allow diffusion of the therapeutic agent into the target location 220. Alternatively, the sheath 210 remains stationary while the catheter 110 moves the expandable portion 120 forward into the occluded region. The sheath 210 protects the agent and coating 130, thus inhibiting premature release of the therapeutic agent.

Detailed Description Paragraph Right (19):
Useful therapeutic applications to which the present invention can be applied include, without limitation, methods for treating, ameliorating, reducing and/or inhibiting any lumen or tissue injury, including those that result in denuding the interior wall of a lumen, namely its endothelial lining, including the lining of a blood vessel, urethra, lung, colon, urethra, biliary tree, esophagus, prostate, fallopian tubes, uterus, vascular graft, or the like. Such injuries result from disease, as in the case of atherosclerosis or urethal hyperplasia (strictures), and/or from mechanical injury from, for example, deployment of an endolumenal stent or a catheter-based device, including balloon angioplasty and related devices.

Detailed Description Paragraph Right (22):
The methods of the present invention can also be used to deliver diagnostic and/or imaging agents, including ultrasound contrasting agents such as perfluorocarbon. Other contrasting agents are well known to those skilled in the art. The contrasting agent is typically a microbubble encapsulated in a lipid, lipid-like or protein coat for catheter-based delivery. The microbubble further can have a tissue-targeting agent on its surface. Once delivered to the site of interest, the microbubble is burst or otherwise detected using ultrasound enhancement. The contrasting agent also can be combined with a therapeutic agent, genetic or otherwise, which then is delivered when the bubble is burst by ultrasound enhancement. Delivery to large surface areas such as lung and uterus interiors can benefit from this protocol.

Detailed Description Paragraph Right (27):
Replication-deficient adenoviral vector gene delivery was accomplished in vivo with the use of both infusion style local delivery catheters and hydrogel coated angioplasty catheters. The infusion based devices were used to deliver viral particles to the vessel wall by pressure driven convection combined with concentration driven diffusion. Transmural hydraulic pressure was created at the vessel wall and modulated using these devices by infusion the viral solution under a known applied pressure. Two infusion devices were used to modulate pressure at a constant delivery time: the Channeled balloon catheter (Boston Scientific Corporation, Natick, Mass.) was used for low to moderate infusion pressures and the Transport catheter (Boston Scientific Corporation, Natick, Mass.) was used for high pressure infusions. Concentration was modulated at a constant infusion pressure of approximately 0.1 atm. Additionally, hydrogel coated angioplasty balloons were used to deliver virus to the vessel wall by a purely concentration driven diffusive mechanism. The hydrogel coated angioplasty balloons were coated with a crosslinked polyacrylic acid polymer.

Detailed Description Paragraph Right (30):
Virus was applied to the hydrogel coating of angioplasty balloons by slowly applying 25 .mu.l of a 1.7.times.10.sup.11 pfu/ml adenoviral .beta.-galactosidase stock solution (replication deficient adenovirus carrying the E coli .beta.-galactosidase gene) onto the coating using a micro-pipette. A 2.0 cm long, 3.0 mm diameter loaded hydrogel coated balloon catheter was placed within a protective sheath and inflated to 2 atm. The entire assembly was advanced over a 0.014 inch guidewire via the right common carotid artery to the bifurcation leading to the external iliacs. The balloon was then deflated and quickly advanced further to either the right or left external iliac artery. Viral delivery was allowed to occur for either 2 or 30 min.

Detailed Description Paragraph Right (37):
The effect of delivery time on gene transfection was examined using hydrogel coated balloons. The balloons were left in contact with the vessel wall for either 2 or 30 minutes. As shown in Table III, transfection efficiency was 1.57.+-.0.05% and 2.04.+-.75% for delivery at 30 minutes and 2 minutes, respectively. In a related set of experiments, 200 .mu.l of viral solution infused through a channeled balloon catheter over 2 minutes followed by no incubation or a 30 minute incubation where the balloon was left inflated. Transfection was 2.53.+-.0.44 and 2.00.+-.0.52 for delivery with or without a 30 minute incubation, respectively.

Detailed Description Paragraph Left (3):
Delivery with a Hydrogel Coated Balloon Catheter

Detailed Description Paragraph Left (5):
A comparable level of gene transfection, 2.04.+-.0.75%, was achieved at zero hydraulic pressure (no infusion volume) when the virus was delivered passively from a hydrogel coated balloon, providing an indication that molecular diffusion rather than convection is the predominant mechanism for viral transport in the vessel wall. Viral infusion volume and pressure were determined not to have a statistically significant effect (p=not significant ("NS")) on transfection efficiency under each condition tested in Table I (all data were compared by a one-way analysis of variants).

CLAIMS:

6. The method of claim 5, further comprising the steps of:

coating said expandable portion with a polymer coating; and

incorporating said therapeutic agent into said polymer coating.

7. The method of claim 6, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrolidone, maleic anhydnde polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosamnoglycans, polysacchaxides, polyesters, polyuretbanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylactic acids, polyglycolic acids, polycaprolactones, polybydroxybutyrate valerates, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, polyacrylic acid, and mixtures and co-polymers thereof.

17. The method of claim 16, further comprising the steps of,

coating said expandable portion with a polymer coating; and

incorporating said therapeutic agent into said polymer coating.

18. The method of claim 17, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyurethanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylactic acids, polyglycolic acids, polycaprolactones, polyhydroxybutyrate valerates, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, polyacrylir acid, and mixtures and co-polymers thereof.

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L7: Entry 8 of 11 File: USPT Jan 18, 2000

DOCUMENT-IDENTIFIER: US 6015432 A
TITLE: Wire reinforced vascular prosthesis

Brief Summary Paragraph Right (3):
Further, it is desirable to have a graft, which does not need a stent placed at one or both ends of the graft, in order to firmly embed the graft into the lumen of the body. Further, naturally, it is desirable to have a device wherein the superelastic material does not protrude from the outside of the graft. In fact, it is most desirable to have a device where the wire is co-extensive with the textile or other material from which the graft is formed.

Brief Summary Paragraph Right (4):
These and other objects of the invention are described by the current device. What is described herein is a endovascular tube or bifurcated prosthesis used for the repair of aneurysms or other vessel disease, which can be either soft or hard occlusive disease. This prosthesis is constructed by fabricating generally a tubular structure that consists of a textile or other polymeric material and through which is threaded a superelastic metal wire such as: nitinol; a ductile wire; or other filament material. The textile can be a polymeric material such as polyethyleneteraphthalate PET or a biocompatible polymer. The wire, if it is superelastic provides the self-expandability of the current device.

Detailed Description Paragraph Right (1):
As can be seen from the figures, a device 10 is formed from a graft material 12. The graft material 12 is a woven mesh such as Dacron.RTM. or a biocompatible graft 12 on polymer graft. Interposed within interstitial spaces of the device 10 is a series of self-expanding wires 14. These wires 14 are generally placed lengthwise as can be seen in FIGS. 1 and 3. However, as in FIG. 2, the wires 14 are placed circumferentially around the graft 10. In either event, it is the self-expandability of nitinol that proves useful to enhance the particular working qualifications of the Dacron.RTM. graft material 12. As seen in FIGS. 3 and 4, in that is the side view and end view figures, it can be shown that the graft 12 is formed so that the wires 14 expand after having been woven through the graft 12. This, of course, causes the device itself to expand upon release within a desired lumen of the body.

Detailed Description Paragraph Right (2):
Typically, the wire 14 is chosen from a self-expanding material such as nitinol. Of course, wire 14 can be made from some other sort of ductile wire or other filament material. The only necessity is that the structural integrity provided by the wire or other filament be interposed within the graft, as can be seen from the weaves of FIGS. 1-4. If a superelastic material is used, such that the graft can be expanded without need for a balloon, then of course the wire will provide a certain advantage over current self expanding stent-graft combinations, that is, an ability to reduce the overall diametral width of the wire/graft device. This is accomplished due to the combined weave and graft occurring in the same diametral thickness.

Detailed Description Paragraph Right (3):
So, as can be readily seen, this design is unique in that the superelastic or ductile wire or other filament material is fully incorporated into the textile structure of the polymer base material. Furthermore, it is unique in that the prosthesis itself can be made to be self-expanding.

Detailed Description Paragraph Right (5):
Depending on the construction and configuration of the supporting backbone material, stents of either superelastic, ductile or combination of materials can be placed on either end of the prosthesis 10 to anchor the prosthesis 10 to the body wall. However, as can be seen, with the current invention, stents are not per se necessary to provide

support to the system.

Detailed Description Paragraph Right (6):
Naturally, because the superelastic nitinol material is provided within the shape of the current device, it is typically thinner than a layered approach using a stent and a graft combination when the wire 14 is placed on the interior (where it is exposed to the interior side of the graft 12) prosthesis 10 is held by force against the luminal wall.

Detailed Description Paragraph Right (8):
In use therefore, the device 10 of the present invention is formed by interweaving a nitinol 14, typically a superelastic nitinol, into a Dacron.RTM. or Teflon.RTM. graft 12. Upon weaving, the device is given a "memory" so that it will take a permanent set at a certain size. Then, the device 10 is compressed into a catheter or other delivery system (not shown) useful for delivering self-expanding stents. When this happens, the device is further compressed and placed in the catheter and furthermore placed in the body. The device is presented to the lesion site in the same way as is done by typical self-expanding stent users. Thereafter, when in place, a sheath (not shown) of the stent delivery system is pulled back, and the device 10 is released. This allows the device 10 to be placed at the lesion site, and with little blood leakage. This provides capable application for either aneurysmal or occlusive disease. Once the prosthesis 10 is in place, the device prevents blood flow and turbulence and pressure on an aneurysm at the situs of graft 10. With respect occlusive disease, the prosthesis 10 can be passed into a lesion of about 1-2.5 mm. By doing so, the occlusive disease (or the aneurysmal area is hopefully well treated.

Detailed Description Paragraph Right (9):
Minor modifications are certainly possible without departing from the scope of the invention. For instance, the wire materials can be substituted to be either stainless steel, stiffer polymer materials, tantalum or cobalt based superalloys. Whereas the superelastic wires are intended to be self-expanding and supporting, other materials can be interwoven or braided as into the prosthesis 10 to create a self-expanding prosthesis. The wires can be placed in such a manner as to obviate the need for stents on one end of the construction, and more typical grafts on the other end. Naturally, the prosthesis itself can either be straight, tapered or bifurcated. The device can be formed into any shape to conform to various vessel configurations and differing anatomies.

Detailed Description Paragraph Right (10):
The invention certainly can be used to treat in other conditions such as TIPPS (trans intrahapetic peripheral prosthetic surgeries), diffusive occlusive disease, and soft tissue occlusions where a covered stent would normally be used. The wire can be coated with a textile material such that the prosthesis itself presents uniform biocompatible surface to the body. Or, multiple types of metal wires can be incorporated into the prosthesis to make it more or less radiopaque, as well as to restrict the superelastic material from over-dilating the vessel wall. Depending on the application, the wire or textile can be coated with therapeutic agents such as rapamycin to enhance or retard endothelization of the prosthesis.

Other Reference Publication (4):
Tantalum-Dacron Coknit Stent for Endovascular Treatment of Aortic Aneurysms: A preliminary Experimental Study, Piquet et al., J. of Vascular Surgery, vol. 19, Apr. 1994, pp. 689-706.

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DOCUMENT-IDENTIFIER: US 5693085 A
TITLE: Stent with collagen

Detailed Description Paragraph Right (31):
When the collagen liner is comprised of two different materials which are joined together as shown in FIG. 10, it may be referred to as a bilayer structure. When placed in a stem, layer 12c is placed luminally with layer 12d contacting the inner surface of the stent. Layer 12d, which may be in contact with the vessel wall through openings in the stent in such an arrangement, is preferably strong and enables the inner luminal layer 12c itself to have the structural integrity necessary to ensure ease of loading, delivery and deployment. Layer 12c may for example be comprised of a collagenous material in the range of 5 to 200 microns thick. Such a biologically derived material may be harvested from a donor source, cleaned of unwanted tissues and formed into the tube by wrapping it around a mandrel and bonding the material to itself. Synthetic materials may be used to comprise the support of layer 12d of the liner, however, vascular graft materials such as PTFE, woven dacron, polyurethane and the like may also be used. Resorbable polymers (PLLA, PGA, PDLLA, PHB, polyanhydrides) are another choice for the support layer 12d of the liner 12. These materials may be formed into a tube by extrusion, solvent casting, injection molding, etc. or spinning into fibers and weaving into a tubular structure. A tube of one of the aforementioned polymers may also be constructed by a non-woven fiber technique.

Detailed Description Paragraph Right (32):
The innermost or luminal side, i.e., layer 12c of the liner serves a different function than the support layer 12d. The luminal surface or layer 12c must be a substrate for the growth of endothelial cells, as well as a reservoir for therapeutic agents. Preferred material is fibular Type I collagen and/or porcine Type IV collagen in the range of 5-200 microns thick, although fibrin may also be used for this purpose. Highly hydrated materials, such as cross linked hydrogels meet the drug holding requirement for the luminal portion of the liner, examples of which are polyethers, polyalcohols, polypyrollidones, polypeptides, polyacids and the like. The layer 12 may also be a mixture of the above materials with a drug binding, ionic or covalent, molecule. One such molecule would be protamine, which effectively ionically binds heparin. These polymers can also be treated with growth factors, such as RGD peptides to promote endothelialization. The preferred method of drug incorporation would involve the preparation of a solution of the therapeutic agent and allowing the dehydrated luminal side of the sleeve to swell with the solution. Upon evaporation of the carrier solvent, the drug would be made to reside in the matrix which comprises the inner layer of the liner, i.e., layer 12c. The device may act as a sponge to soak-up a drug in solution and to elute it from the stent upon implantation.

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=OR		
L13	stent and (polyanhy$ or lactone$)and carrier and coat$	125	L13
L12	stent and (polyanhy$ or lactone$)and coat$	248	L12
L11	polymer same carrier$ same stent and polyanhy$	7	L11
L10	polymer adj4 carrier$ same stent and polyanhy$	2	L10
L9	polymer adj4 carrier$ same stent and lactone	0	L9
L8	polymer adj4 carrier$ same stent	27	L8
L7	rapamycin and stent and polymer	11	L7
L6	rapamycin and (stent or graft)and coat$ and polymer same carrier	24	L6
L5	rapamycin and (stent or graft)and coat$ and polymer	89	L5
L4	rapamycin and (stent or graft)and polymer	120	L4
L3	rapamycin and (stent or graft)	488	L3
L2	rapamycin and stent	22	L2
L1	rapamycin	871	L1

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